Clinical trial results:
Randomized Phase III Study of Intensive Chemotherapy with or without Dasatinib (Sprycel™) in Adult Patients with Newly Diagnosed Core-Binding Factor Acute Myeloid Leukemia (CBF-AML)
AMLSG 21-13

Summary

EudraCT number	2013-003117-18
Trial protocol	DE AT
Global end of trial date	19 February 2024

Results information

Result version number	v1 (current)
This version publication date	21 February 2025
First version publication date	21 February 2025
Summary attachment (see zip file)	AMLSG 21-13_Final report (AMLSG_21-13_Final_report_BfArM.pdf)

Trial information

Trial identification

Sponsor protocol code	AMLSG21-13

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02013648
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Ulm
Sponsor organisation address	Albert-Einstein-Allee 29, Ulm, Germany, 89081
Public contact	AMLSG Studienzentrale, Universitätsklinikum Ulm, +49 731500 45715, aml.sekretariat@uniklinik-ulm.de
Scientific contact	AMLSG Studienzentrale, Universitätsklinikum Ulm, +49 731500 45715, aml.sekretariat@uniklinik-ulm.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 November 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 February 2024
Global end of trial reached?	Yes
Global end of trial date	19 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Efficacy Objective
- To assess event-free survival (EFS) after intensive induction (daunorubicin and cytarabine) and consolidation (high-dose cytarabine) chemotherapy with or without dasatinib in patients with CBF-AML

Secondary Objectives
- To assess the interaction between type of CBF-AML [t(8;21) 3versus inv(16)] and randomization accordingly on all survival endpoints
- To assess cumulative incidence of relapse (CIR) and death (CID)
- To assess relapse-free (RFS) and overall survival (OS)
- To assess outcome according to KIT mutational status
- To assess pharmacodynamic inhibition of KIT
- To assess toxicity

Protection of trial subjects:

In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, chest X-ray, echo scan, physical examination findings, monitoring of concomitant therapy. For each safety parameter, all findings (whether normal or abnormal) were recorded in the eCRF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 30
Country: Number of subjects enrolled	Germany: 174
Worldwide total number of subjects	204
EEA total number of subjects	204

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	176
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient in: 29.08.2014
Last patient last visit: 19.02.2024
Recruitment was not interrupted during the study.

Pre-assignment

Screening details:

Molecular genetic analysis (central AMLSG reference lab) of blood and bone marrow was performed at baseline within 48 hours to make an enrollment possible.

Pre-assignment period milestones

Number of subjects started	204
Number of subjects completed	202

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 2

Period 1

Period 1 title	Overall trial period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Standard

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the first induction cycle, cytarabine was administered by continuous intravenous infusion in a dose of 200 mg/m2 from day 1 to day 7. In the (optional) second induction cycle, cytarabine was administered by
intravenous infusion in a dose of 200mg/m2 from day 1 to day 5. In all consolidation cycles, cytarabine was administered by intravenous infusion in a dose of 3 g/m2 twice a day on days 1, 2 and 3. For patients > 60 years of age, dose of cytarabine was reduced to 1 g/m2.

Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the first induction cycle, daunorubicin was administered by in a dose of 60 mg/m2 on
days 1, 2 and 3. In an optional second induction cycle, daunorubicin was administered in a dose of 50 mg/m2 on days 1,2 and 3.

Arm title	Arm B: Dasatinib

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the first induction cycle, cytarabine was administered by continuous intravenous infusion in a dose of 200 mg/m2 from day 1 to day 7. In the (optional) second induction cycle, cytarabine was administered by
intravenous infusion in a dose of 200mg/m2 from day 1 to day 5. In all consolidation cycles, cytarabine was administered by intravenous infusion in a dose of 3 g/m2 twice a day on days 1, 2 and 3. For patients > 60 years of age, dose of cytarabine was reduced to 1 g/m2.

Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the first induction cycle, daunorubicin was administered by in a dose of 60 mg/m2 on
days 1, 2 and 3. In an optional second induction cycle, daunorubicin was administered in a dose of 50 mg/m2 on days 1,2 and 3.

Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dasatinib was administered in a dose of 100 mg daily on days 8 to 21 in the first induction cycle and on days 6 to 21 in the second induction cycle. In the consolidation cycles, 100 mg dasatinib was administered on days 4 to 28.
After consolidation therapy, patients received one year of dasatinib maintenance therapy (100 mg per day).

Number of subjects in period 1[1]	Arm A: Standard	Arm B: Dasatinib
Started	102	100
Completed	74	27
Not completed	28	73
Adverse event, serious fatal	5	5
Consent withdrawn by subject	9	15
Adverse event, non-fatal	4	27
Other reasons	5	10
Lack of efficacy	4	15
Protocol deviation	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: N=204 patients were enrolled overall into the trial. Two patients were excluded due to violation of inclusion/exclusion criteria (invalid informed consent) and therefore were not included into the Intention-to-treat population which represents the baseline population.

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Standard
Reporting group description: -	
Reporting group title	Arm B: Dasatinib
Reporting group description: -	

Reporting group values	Arm A: Standard	Arm B: Dasatinib	Total
Number of subjects	102	100	202
Age categorical Units: Subjects			
18-60 years	82	78	160
>60 years	20	22	42
Age continuous Units: years			
median	48.9	49.7	
full range (min-max)	18.3 to 75.7	18.2 to 77.0	-
Gender categorical Units: Subjects			
Female	51	56	107
Male	51	44	95
CBF Type Units: Subjects			
inv(16)	53	55	108
t(8;21)	49	45	94
Type of AML Units: Subjects			
deNovo AML	95	84	179
secondary AML	1	3	4
therapy-related AML	5	12	17
Not recorded	1	1	2
KIT mutation status Units: Subjects			
Mutation	32	26	58
Wildtype	70	74	144
FLT3-ITD mutation status Units: Subjects			
Positive	4	1	5
Negative	98	99	197
FLT3-TKD mutation status Units: Subjects			
Positive	10	11	21
Negative	92	89	181
ECOG Performance Status Units: Subjects			
ECOG 0	50	61	111
ECOG 1	40	33	73

ECOG 2	7	5	12
Not recorded	5	1	6

White blood cell count (diagnosis)			
Units: Giga/l			
median	12.5	9.72	
full range (min-max)	0.5 to 177	0.31 to 205	-
Hemoglobin			
Units: g/dl			
median	8.8	9.1	
full range (min-max)	3.6 to 14.0	4.2 to 15.4	-
Platelet count			
Units: Giga/l			
median	36	40	
full range (min-max)	5 to 247	6 to 230	-
LDH			
Units: U/l			
median	503	416	
full range (min-max)	133 to 2610	5 to 2940	-
Bone marrow blasts			
Units: Percentage			
median	53	60	
full range (min-max)	5 to 95	5 to 100	-
Peripheral blood blasts			
Units: Percentage			
median	33	31.5	
full range (min-max)	0 to 82	0 to 90	-
Height			
Units: cm			
median	171	173	
full range (min-max)	152 to 203	152 to 193	-
Weigth			
Units: kg			
median	82	77	
full range (min-max)	47 to 138	50 to 147	-

End points

End points reporting groups

Reporting group title	Arm A: Standard
Reporting group description: -	
Reporting group title	Arm B: Dasatinib
Reporting group description: -	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients with a valid informed consent. Not included in ITT were patients who withdraw informed consent before start of treatment. Patients in this population were analysed according to the treatment arm assigned at randomization.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population included all patients of the ITT population who received at least one dose or part of a dose of one of the study medications (Daunorubicin, Idarubicin, Cytarabine, Dasatinib) during the treatment phase.

Primary: Event-free Survival

End point title	Event-free Survival

End point description:

The primary endpoint of the study was event-free survival; an event was defined as one of the following:

- Refractory disease, defined as failure to achieve at least a PR after the first induction cycle and CR or CRi after an optional second induction cycle
- Death by any cause
- Hematologic Relapse
- Molecular persistence
- Molecular relapse.

End point type	Primary

End point timeframe:

after 48 months

End point values	Arm A: Standard	Arm B: Dasatinib	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	102	100	202	
Units: %				
number (confidence interval 95%)	41 (32 to 52)	44 (35 to 56)	42 (36 to 50)	

Attachments (see zip file)	Event-free survival_overall/EFS overall.jpg Event-free survival_ according treatment/EFS treatment.jpg EFS_according KIT mutation

Statistical analyses

Statistical analysis title	Primary analysis Event-free survival (univariate)

Statistical analysis description:

The EFS is formally compared between treatment arms using the stratified logrank test with strata of patient age at registration (≤ 60 years vs >60 years) and CBF-AML type (t(8;21) vs inv(16)).

Comparison groups	Arm B: Dasatinib v Arm A: Standard
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.33

Statistical analysis title	Event-free survival (multivariate)
Comparison groups	Arm A: Standard v Arm B: Dasatinib
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.995 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.48

Notes:

[1] - Multivariable analysis adjusted for the following potential prognostic covariates:
- Age, Sex
- Eastern Cooperative Oncology Group (ECOG) status (0-1 vs. 2+)
- WBC (log-10 transformed)
- KIT mutation status
- FLT3 mutation status
- AML Type (de novo vs.secondary/therapy-related)
- CBF type (inv(16) vs. t(8;21))
- Minimal residual disease status (MRD at low level/negative vs. positive as time-dependent covariate)

[2] - No significant treatment effect, but negative prognostic effects for higher white blood cell count (HR for log10 increase 2.01; p<.001), KIT status (HR 1.96; p=0.002) and in trend for MRD positivity (HR 1.66; p=0.052).

Statistical analysis title	Subgroup analysis: KIT mutation
Comparison groups	Arm A: Standard v Arm B: Dasatinib

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.73

Statistical analysis title	Subgroup analysis: KIT wildtype
Comparison groups	Arm B: Dasatinib v Arm A: Standard
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.59

Statistical analysis title	Analysis of interaction effect on EFS
Comparison groups	Arm B: Dasatinib v Arm A: Standard
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.322
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.47

Notes:

[3] - Interaction effect between treatment arm and CBF-AML type

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival (OS), defined as the time from the date of randomization to the date of death due to any cause. For patients who were still alive and patients who were lost to follow up, OS was censored at the date they were last known to be alive (latest at the end of study).

End point type	Secondary

End point timeframe:

48 months

End point values	Arm A: Standard	Arm B: Dasatinib	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	102	100	202	
Units: %				
number (confidence interval 95%)	76 (68 to 85)	78 (70 to 87)	77 (71 to 83)	

Attachments (see zip file)	Overall survival_overall/os overall.jpg Overall survival_according treatment/os treatment.jpg Overall survival_KIT status/fig_OS_subgrps_KIT_mutation.

Statistical analyses

Statistical analysis title	Overall survival (univariate)
Comparison groups	Arm B: Dasatinib v Arm A: Standard
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.63

Statistical analysis title	Overall survival (multivariate)
Comparison groups	Arm A: Standard v Arm B: Dasatinib

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.887
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.79

Notes:

[4] - Multivariable analysis models were adjusted for the following potential prognostic covariates:
- Age, Sex
- Eastern Cooperative Oncology Group (ECOG) status (0-1 vs. 2+)
- WBC (log-10 transformed)
- KIT mutation status
- FLT3 mutation status
- AML Type (de novo vs.secondary/therapy-related)
- CBF type (inv(16) vs. t(8;21))
- Minimal residual disease status (MRD at low level/negative vs. positive as time-dependent covariate)

Statistical analysis title	Subgroup analysis: KIT mutation
Comparison groups	Arm A: Standard v Arm B: Dasatinib
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	1.75

Statistical analysis title	Subgroup analysis: KIT wildtype
Comparison groups	Arm B: Dasatinib v Arm A: Standard
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	2.27

Statistical analysis title	Interaction analysis OS
Statistical analysis description:	
Interaction effect between treatment arm and CBF-AML type	
Comparison groups	Arm B: Dasatinib v Arm A: Standard
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.383
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	1.97

Secondary: Relapse-free survival (RFS)

End point title	Relapse-free survival (RFS)
End point description:	
Relapse-free survival (RFS) was defined as the time from first CR/CRi until hematologic/ molecular relapse or molecular persistence or death, whichever comes first.	
End point type	Secondary
End point timeframe:	
48 months	

End point values	Arm A: Standard	Arm B: Dasatinib	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	98	91	189	
Units: %				
number (confidence interval 95%)	42 (33 to 54)	49 (39 to 61)	45 (39 to 53)	

Attachments (see zip file)	Relapse-free survival _overall/RFS overall.jpg Relapse-free survival_according treatment/RFS_treatment.jpg

RFS_according KIT mutation

Statistical analyses

Statistical analysis title	Relapse-free survival (univariate)
Comparison groups	Arm B: Dasatinib v Arm A: Standard
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.21

Statistical analysis title	Relapse-free survival (multivariate)
Comparison groups	Arm B: Dasatinib v Arm A: Standard
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.494 [6]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.32

Notes:

[5] - Multivariable analysis models were adjusted for the following potential prog- nostic covariates:
- Age, Sex
- Eastern Cooperative Oncology Group (ECOG) status (0-1 vs. 2+)
- WBC (log-10 transformed)
- KIT mutation status
- FLT3 mutation status
- AML Type (de novo vs.secondary/therapy-related)
- CBF type (inv(16) vs. t(8;21))
- Minimal residual disease status (MRD at low level/negative vs. positive as time-dependent covariate)

[6] - No signifcant treatment effect, but negative effect on EFS for higher white blood cell count (HR for log10 increase 2.21; p<.001), KIT status (HR 2.15; p<.001) and presence of CBF-AML type t(8;21) (HR 1.58; p=0.048).

Statistical analysis title	Interaction analysis RFS
Comparison groups	Arm A: Standard v Arm B: Dasatinib

Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.264
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.44

Statistical analysis title	Subgroup analysis: KIT mutation
Comparison groups	Arm A: Standard v Arm B: Dasatinib
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.63

Statistical analysis title	Subgroup analysis: KIT wildtype
Comparison groups	Arm A: Standard v Arm B: Dasatinib
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.63

Secondary: Cumulative incidence of relapse (CIR)

End point title	Cumulative incidence of relapse (CIR)

End point description:

The analyses of CIR and CID are restricted to patients in the ITT population who achieved CR/CRi. CIR and CID are analysed using a competing risks model for time to relapse (TTR) and non- relapse mortality (NRM). TTR is defined as the time from first CR/CRi to until hematologic/ molecular relapse or molecular persistence. Deaths in remission are considered as a competing event. NRM is defined as the time from achievement of a remission (CR/CRi) to death without prior re- lapse or molecular persistence. Relapse or molecular persistence after achieving CR/CRi are considered as a competing event. Patients who are not known to have relapsed, being molecularly persistent or died are censored at the date of last clinical response assessment for both endpoints.

End point type	Secondary

End point timeframe:

48 months

End point values	Arm A: Standard	Arm B: Dasatinib	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	98	91	189	
Units: %				
number (confidence interval 95%)	52 (42 to 62)	47 (36 to 57)	50 (42 to 57)	

Attachments (see zip file)	CIR_CID_overall/CIR_CID overall.jpg CIR_CID_according treatment/CIR_CID treatment.jpg

Statistical analyses

Statistical analysis title	Cumulative incidence of relapse (univariate)
Comparison groups	Arm B: Dasatinib v Arm A: Standard
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Gray's test

Secondary: Cumulative incidence of death in CR/CRi (CID)

End point title	Cumulative incidence of death in CR/CRi (CID)

End point description:

The analyses of CIR and CID are restricted to patients in the ITT population who achieved CR/CRi. CIR and CID are analysed using a competing risks model for time to relapse (TTR) and non- relapse mortality (NRM). TTR is defined as the time from first CR/CRi to until hematologic/ molecular relapse or molecular persistence. Deaths in remission are considered as a competing event. NRM is defined as the time from achievement of a remission (CR/CRi) to death without prior re- lapse or molecular persistence. Relapse or molecular persistence after achieving CR/CRi are considered as a competing event. Patients who are not known to have relapsed, being molecularly persistent or died are censored at the date of last clinical response assessment for both endpoints.

End point type	Secondary

End point timeframe:
48 months

End point values	Arm A: Standard	Arm B: Dasatinib	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	98	91	189	
Units: %				
number (confidence interval 95%)	5 (1 to 10)	5 (0 to 9)	5 (2 to 8)	

Attachments (see zip file)	CIR_CID_overall/CIR_CID overall.jpg CIR_CID_according treatment/CIR_CID treatment.jpg

Statistical analyses

Statistical analysis title	Cumulative incidence of death (univariate)
Comparison groups	Arm B: Dasatinib v Arm A: Standard
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96
Method	Gray's test

Secondary: Hematological recovery induction cycle 1

End point title	Hematological recovery induction cycle 1

End point description:

		Arm A: Standard N = 107		Arm B: Dasatinib N = 93	
Component	Time [days]	Rate	95%-CI	Rate	95%-CI
ANC recovery (≥0.5 G/l)	28	0.61	(0.51, 0.70)	0.57	(0.46, 0.67)
ANC recovery (≥1.5 G/l)	28	0.39	(0.29, 0.48)	0.36	(0.26, 0.47)
WBC recover (≥1.0 G/l)	28	0.83	(0.74, 0.89)	0.79	(0.69, 0.87)
Platelet recovery (≥50 G/l)	28	0.87	(0.79, 0.92)	0.78	(0.68, 0.85)
Platelet recovery (≥100 G/l)	28	0.79	(0.70, 0.86)	0.68	(0.57, 0.77)

End point type	Secondary
End point timeframe:	
Induction cycle 1	

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	200			
Units: recovery rate				
number (confidence interval 95%)	0 (0 to 0)			

Attachments (see zip file)	Hem recovery_induction1/hemrecov_ind1-1.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Hematological recovery induction cycle 2

End point title	Hematological recovery induction cycle 2

End point description:

Component	Time [days]	Arm A: Standard N = 17 Rate	95%-CI	Arm B: Dasatinib N = 12 Rate	95%-CI
ANC recovery (≥0.5 G/l)	28	0.74	(0.45, 0.89)	0.63	(0.29, 0.84)
ANC recovery (≥1.5 G/l)	28	0.49	(0.24, 0.70)	0.39	(0.12, 0.66)
WBC recover (≥1.0 G/l)	28	0.88	(0.61, 0.97)	0.92	(0.54, 0.99)
Platelet recovery (≥50 G/l)	28	0.88	(0.59, 0.97)	0.92	(0.54, 0.99)
Platelet recovery (≥100 G/l)	28	0.79	(0.49, 0.92)	0.92	(0.54, 0.99)

End point type	Secondary

End point timeframe:

Induction cycle 2

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: rate				
number (confidence interval 95%)	0 (0 to 0)			

Attachments (see zip file)	Hem recovery_induction2/hemrecov_ind2-1.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Hematological recovery consolidation cycle 1

End point title	Hematological recovery consolidation cycle 1

End point description:

	Arm A: Standard N = 96	Arm B: Dasatinib N = 77

Component	Time [days]	Rate	95%-CI	Rate	95%-CI
ANC recovery (≥0.5 G/l)	28	0.80	(0.70, 0.87)	0.83	(0.71, 0.90)
ANC recovery (≥1.5 G/l)	28	0.66	(0.55, 0.75)	0.65	(0.52, 0.75)
WBC recovery (≥1.0 G/l)	28	0.94	(0.86, 0.97)	0.97	(0.90, 0.99)
Platelet recovery (≥50 G/l)	28	0.79	(0.69, 0.86)	0.89	(0.78, 0.94)
Platelet recovery (≥100 G/l)	28	0.60	(0.49, 0.69)	0.75	(0.63, 0.84)

End point type	Secondary

End point timeframe:

Consolidation cycle 1

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	173			
Units: rate				
number (confidence interval 95%)	0 (0 to 0)			

Attachments (see zip file)	Hem recovery_consolidation 1/unnamed-chunk-cons1-3.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Hematological recovery consolidation cycle 2

End point title	Hematological recovery consolidation cycle 2

End point description:

		Arm A: Standard N = 94		Arm B: Dasatinib N = 71	
Component	Time [days]	Rate	95%-CI	Rate	95%-CI
ANC recovery (≥0.5 G/l)	28	0.75	(0.64, 0.82)	0.78	(0.66, 0.87)
ANC recovery (≥1.5 G/l)	28	0.50	(0.40, 0.60)	0.65	(0.52, 0.75)
WBC recovery (≥1.0 G/l)	28	0.88	(0.79, 0.93)	0.97	(0.89, 0.99)
Platelet recovery (≥50 G/l)	28	0.59	(0.48, 0.68)	0.79	(0.67, 0.87)
Platelet recovery (≥100 G/l)	28	0.43	(0.32, 0.53)	0.55	(0.42, 0.66)

End point type	Secondary

End point timeframe:

Consolidation cycle 2

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	165			
Units: %				
number (confidence interval 95%)	0 (0 to 0)			

Attachments (see zip file)	Hem recovery_consolidation 2/unnamed-chunk-cons24.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Hematological recovery consolidation cycle 3

End point title	Hematological recovery consolidation cycle 3

End point description:

		Arm A: Standard N = 94		Arm B: Dasatinib N = 64	
Component	Time [days]	Rate	95%-CI	Rate	95%-CI
ANC recovery (≥0.5 G/l)	28	0.81	(0.72, 0.88)	0.84	(0.72, 0.92)
ANC recovery (≥1.5 G/l)	28	0.59	(0.48, 0.68)	0.74	(0.60, 0.84)
WBC recovery (≥1.0 G/l)	28	0.93	(0.86, 0.97)	0.98	(0.89, 1.00)
Platelet recovery (≥50 G/l)	28	0.64	(0.53, 0.73)	0.60	(0.47, 0.71)
Platelet recovery (≥100 G/l)	28	0.42	(0.31, 0.52)	0.40	(0.28, 0.52)

End point type	Secondary

End point timeframe:

Consolidation cycle 3

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	158			
Units: rate				
number (confidence interval 95%)	0 (0 to 0)			

Attachments (see zip file)	Hem recovery_consolidation 3/unnamed-chunk-cons3-5.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Hematological recovery consolidation cycle 4

End point title	Hematological recovery consolidation cycle 4

End point description:

		Arm A: Standard N = 85		Arm B: Dasatinib N = 57	
Component	Time [days]	Rate	95%-CI	Rate	95%-CI
ANC recovery (≥0.5 G/l)	28	0.82	(0.71, 0.89)	0.82	(0.69, 0.90)
ANC recovery (≥1.5 G/l)	28	0.56	(0.45, 0.66)	0.61	(0.47, 0.73)

WBC recovery (≥1.0 G/l)	28	0.94	(0.86, 0.97)	0.91 (0.80, 0.96)
Platelet recovery (≥50 G/l)	28	0.58	(0.47, 0.68)	0.62 (0.47, 0.73)
Platelet recovery (≥100 G/l)	28	0.31	(0.21, 0.41)	0.49 (0.35, 0.61)

End point type	Secondary

End point timeframe:

Consolidation cycle 4

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	142			
Units: %				
number (confidence interval 95%)	0 (0 to 0)			

Attachments (see zip file)	hematologic recovery consolidation cycle 4/unnamed-chunk-

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Early / Hypoplastic Death (ED/HD)

End point title	Rate of Early / Hypoplastic Death (ED/HD)

End point description:

End point type	Secondary

End point timeframe:

Induction therapy

End point values	Arm A: Standard	Arm B: Dasatinib	Safety population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	101	99	200	
Units: Rate				
number (confidence interval 95%)	0.02 (0.005 to 0.07)	0.03 (0.01 to 0.09)	0.03 (0.01 to 0.06)	

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free survival (alternative definition)

End point title	Event-free survival (alternative definition)

End point description:

Event-free survival additionally was analyzed utilizing the following alternative definition of EFS:
EFS was calculated as the time from randomization until failure to achieve CR or CRi after induction, death after achieving CR or CRi, or relapse after achieving CR or CRi, whichever comes first. Patients without CR/CRi after induction were considered as events at the date of the assessment confirming no CR/CRi (as opposed to the original definition of EFS, where patients without CR/CRi after induction were considered as having events at day 1 of randomization). Patients still in first CR/CRi and alive or lost to follow-up wer censored at the date of last response evaluation.

End point type	Secondary

End point timeframe:

48 months

End point values	Arm A: Standard	Arm B: Dasatinib	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	102	100	202	
Units: %				
number (confidence interval 95%)	57 (48 to 68)	55 (46 to 66)	56 (50 to 64)	

Attachments (see zip file)	EFS_alternative definition_overall/EFS_alternative.jpg EFS_alternative definition_acc

Statistical analyses

Statistical analysis title	EFS alternative definition (univariate)
Comparison groups	Arm A: Standard v Arm B: Dasatinib
Number of subjects included in analysis	202
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.76
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.62

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event reporting period began upon signing of informed consent and ended 28 days after the last treatment administration or until all drug-related toxicities were resolved, or until the Investigators assessed AEs as chronic or stable.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Arm A: Standard
Reporting group description: -	
Reporting group title	Arm B: Dasatinib
Reporting group description: -	

Serious adverse events	Arm A: Standard	Arm B: Dasatinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 101 (35.64%)	63 / 99 (63.64%)	
number of deaths (all causes)	5	5	
number of deaths resulting from adverse events	5	5	
Vascular disorders			
Angiopathy			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgery			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Diarrhoea			

subjects affected / exposed	0 / 101 (0.00%)	4 / 99 (4.04%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Administration site reaction			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 101 (1.98%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Pyrexia			
subjects affected / exposed	2 / 101 (1.98%)	9 / 99 (9.09%)	
occurrences causally related to treatment / all	1 / 2	5 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Allergic reaction to excipient			
subjects affected / exposed	0 / 101 (0.00%)	3 / 99 (3.03%)	
occurrences causally related to treatment / all	0 / 0	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			

subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	0 / 101 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 101 (0.00%)	4 / 99 (4.04%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	6 / 101 (5.94%)	4 / 99 (4.04%)	
occurrences causally related to treatment / all	3 / 6	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary hemorrhage			

subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 101 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 101 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigation abnormal			
subjects affected / exposed	0 / 101 (0.00%)	3 / 99 (3.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 101 (0.00%)	4 / 99 (4.04%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	3 / 101 (2.97%)	6 / 99 (6.06%)	
occurrences causally related to treatment / all	4 / 4	12 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight increased			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 101 (0.99%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 101 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			

subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 101 (0.99%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	2 / 2	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	5 / 101 (4.95%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	5 / 6	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ileus			
subjects affected / exposed	0 / 101 (0.00%)	3 / 99 (3.03%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			

subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 101 (0.99%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 101 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			

subjects affected / exposed	0 / 101 (0.00%)	2 / 99 (2.02%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	2 / 101 (1.98%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 101 (0.99%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 101 (0.99%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 101 (1.98%)	6 / 99 (6.06%)	
occurrences causally related to treatment / all	4 / 4	3 / 8	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pleural infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 101 (3.96%)	13 / 99 (13.13%)	
occurrences causally related to treatment / all	2 / 4	8 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rhinitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	10 / 101 (9.90%)	5 / 99 (5.05%)	
occurrences causally related to treatment / all	6 / 11	5 / 5	
deaths causally related to treatment / all	1 / 3	0 / 0	
Skin infection			

subjects affected / exposed	2 / 101 (1.98%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 101 (0.99%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm A: Standard	Arm B: Dasatinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	100 / 101 (99.01%)	99 / 99 (100.00%)	
Vascular disorders			
Embolism			
subjects affected / exposed	6 / 101 (5.94%)	3 / 99 (3.03%)	
occurrences (all)	8	9	
Haematoma			
subjects affected / exposed	13 / 101 (12.87%)	6 / 99 (6.06%)	
occurrences (all)	22	12	
Hypertension			
subjects affected / exposed	12 / 101 (11.88%)	18 / 99 (18.18%)	
occurrences (all)	24	51	
Hypotension			
subjects affected / exposed	19 / 101 (18.81%)	21 / 99 (21.21%)	
occurrences (all)	24	28	
General disorders and administration site conditions			
Administration site reaction			
subjects affected / exposed	7 / 101 (6.93%)	10 / 99 (10.10%)	
occurrences (all)	16	15	
Chills			
subjects affected / exposed	13 / 101 (12.87%)	12 / 99 (12.12%)	
occurrences (all)	15	26	
Fatigue			
subjects affected / exposed	29 / 101 (28.71%)	35 / 99 (35.35%)	
occurrences (all)	54	100	
General disorder			
subjects affected / exposed	7 / 101 (6.93%)	9 / 99 (9.09%)	
occurrences (all)	15	13	
Influenza like illness			
subjects affected / exposed	1 / 101 (0.99%)	6 / 99 (6.06%)	
occurrences (all)	1	9	
Injection site reaction			
subjects affected / exposed	15 / 101 (14.85%)	8 / 99 (8.08%)	
occurrences (all)	31	12	
Pain			

subjects affected / exposed	51 / 101 (50.50%)	43 / 99 (43.43%)	
occurrences (all)	122	87	
Pyrexia			
subjects affected / exposed	67 / 101 (66.34%)	64 / 99 (64.65%)	
occurrences (all)	171	201	
Immune system disorders			
Allergic reaction to excipient			
subjects affected / exposed	17 / 101 (16.83%)	15 / 99 (15.15%)	
occurrences (all)	30	17	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	23 / 101 (22.77%)	27 / 99 (27.27%)	
occurrences (all)	39	44	
Dyspnoea			
subjects affected / exposed	16 / 101 (15.84%)	20 / 99 (20.20%)	
occurrences (all)	22	33	
Epistaxis			
subjects affected / exposed	24 / 101 (23.76%)	18 / 99 (18.18%)	
occurrences (all)	37	24	
Oropharyngeal pain			
subjects affected / exposed	15 / 101 (14.85%)	11 / 99 (11.11%)	
occurrences (all)	25	14	
Pleural effusion			
subjects affected / exposed	2 / 101 (1.98%)	16 / 99 (16.16%)	
occurrences (all)	2	23	
Pneumonitis			
subjects affected / exposed	7 / 101 (6.93%)	8 / 99 (8.08%)	
occurrences (all)	10	9	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 101 (9.90%)	12 / 99 (12.12%)	
occurrences (all)	12	15	
Depression			
subjects affected / exposed	7 / 101 (6.93%)	11 / 99 (11.11%)	
occurrences (all)	10	31	
Insomnia			

subjects affected / exposed	31 / 101 (30.69%)	29 / 99 (29.29%)	
occurrences (all)	81	70	
Restlessness			
subjects affected / exposed	4 / 101 (3.96%)	7 / 99 (7.07%)	
occurrences (all)	7	8	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	12 / 101 (11.88%)	14 / 99 (14.14%)	
occurrences (all)	39	52	
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 101 (7.92%)	12 / 99 (12.12%)	
occurrences (all)	22	26	
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 101 (5.94%)	8 / 99 (8.08%)	
occurrences (all)	16	10	
Blood lactate dehydrogenase increased			
subjects affected / exposed	8 / 101 (7.92%)	9 / 99 (9.09%)	
occurrences (all)	25	23	
C-reactive protein increased			
subjects affected / exposed	20 / 101 (19.80%)	21 / 99 (21.21%)	
occurrences (all)	50	60	
Gamma-glutamyltransferase increased			
subjects affected / exposed	13 / 101 (12.87%)	10 / 99 (10.10%)	
occurrences (all)	35	28	
Investigation abnormal			
subjects affected / exposed	11 / 101 (10.89%)	15 / 99 (15.15%)	
occurrences (all)	16	27	
Neutrophil count decreased			
subjects affected / exposed	68 / 101 (67.33%)	71 / 99 (71.72%)	
occurrences (all)	226	263	
Platelet count decreased			
subjects affected / exposed	95 / 101 (94.06%)	92 / 99 (92.93%)	
occurrences (all)	477	452	
Prothrombin time prolonged			

subjects affected / exposed	6 / 101 (5.94%)	3 / 99 (3.03%)	
occurrences (all)	10	5	
Vitamin D decreased			
subjects affected / exposed	7 / 101 (6.93%)	1 / 99 (1.01%)	
occurrences (all)	18	2	
Weight decreased			
subjects affected / exposed	5 / 101 (4.95%)	6 / 99 (6.06%)	
occurrences (all)	6	6	
Weight increased			
subjects affected / exposed	22 / 101 (21.78%)	21 / 99 (21.21%)	
occurrences (all)	43	36	
White blood cell count decreased			
subjects affected / exposed	93 / 101 (92.08%)	84 / 99 (84.85%)	
occurrences (all)	438	378	
Hypocalcaemia			
subjects affected / exposed	10 / 101 (9.90%)	14 / 99 (14.14%)	
occurrences (all)	11	19	
Hypokalaemia			
subjects affected / exposed	51 / 101 (50.50%)	53 / 99 (53.54%)	
occurrences (all)	113	107	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	6 / 101 (5.94%)	6 / 99 (6.06%)	
occurrences (all)	7	8	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 101 (0.99%)	7 / 99 (7.07%)	
occurrences (all)	1	10	
Cardiac disorder			
subjects affected / exposed	6 / 101 (5.94%)	4 / 99 (4.04%)	
occurrences (all)	9	4	
Sinus tachycardia			
subjects affected / exposed	95 / 101 (94.06%)	10 / 99 (10.10%)	
occurrences (all)	15	17	
Nervous system disorders			

Dizziness			
subjects affected / exposed	10 / 101 (9.90%)	12 / 99 (12.12%)	
occurrences (all)	15	13	
Headache			
subjects affected / exposed	38 / 101 (37.62%)	35 / 99 (35.35%)	
occurrences (all)	117	95	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	95 / 101 (94.06%)	91 / 99 (91.92%)	
occurrences (all)	457	490	
Febrile neutropenia			
subjects affected / exposed	49 / 101 (48.51%)	49 / 99 (49.49%)	
occurrences (all)	99	127	
Haematological disorders			
subjects affected / exposed	6 / 101 (5.94%)	2 / 99 (2.02%)	
occurrences (all)	6	2	
Leukocytosis			
subjects affected / exposed	4 / 101 (3.96%)	9 / 99 (9.09%)	
occurrences (all)	5	12	
Thrombocytosis			
subjects affected / exposed	6 / 101 (5.94%)	3 / 99 (3.03%)	
occurrences (all)	7	4	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 101 (2.97%)	6 / 99 (6.06%)	
occurrences (all)	5	10	
Eye disorders			
Dry eye			
subjects affected / exposed	9 / 101 (8.91%)	2 / 99 (2.02%)	
occurrences (all)	19	3	
Eye disorder			
subjects affected / exposed	6 / 101 (5.94%)	11 / 99 (11.11%)	
occurrences (all)	7	14	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	23 / 101 (22.77%)	27 / 99 (27.27%)	
occurrences (all)	30	44	

Abdominal pain upper			
subjects affected / exposed	16 / 101 (15.84%)	18 / 99 (18.18%)	
occurrences (all)	28	26	
Anal hemorrhage			
subjects affected / exposed	1 / 101 (0.99%)	6 / 99 (6.06%)	
occurrences (all)	1	7	
Colitis			
subjects affected / exposed	2 / 101 (1.98%)	10 / 99 (10.10%)	
occurrences (all)	2	13	
Constipation			
subjects affected / exposed	29 / 101 (28.71%)	40 / 99 (40.40%)	
occurrences (all)	63	74	
Diarrhoea			
subjects affected / exposed	48 / 101 (47.52%)	68 / 99 (68.69%)	
occurrences (all)	72	130	
Dysphagia			
subjects affected / exposed	7 / 101 (6.93%)	2 / 99 (2.02%)	
occurrences (all)	7	3	
Flatulence			
subjects affected / exposed	7 / 101 (6.93%)	11 / 99 (11.11%)	
occurrences (all)	7	24	
Gastrointestinal disorder			
subjects affected / exposed	10 / 101 (9.90%)	8 / 99 (8.08%)	
occurrences (all)	17	10	
Gastrointestinal pain			
subjects affected / exposed	8 / 101 (7.92%)	8 / 99 (8.08%)	
occurrences (all)	11	8	
Haemorrhoids			
subjects affected / exposed	6 / 101 (5.94%)	7 / 99 (7.07%)	
occurrences (all)	10	12	
Nausea			
subjects affected / exposed	64 / 101 (63.37%)	71 / 99 (71.72%)	
occurrences (all)	182	193	
Stomatitis			
subjects affected / exposed	33 / 101 (32.67%)	34 / 99 (34.34%)	
occurrences (all)	43	50	

Toothache			
subjects affected / exposed	6 / 101 (5.94%)	7 / 99 (7.07%)	
occurrences (all)	8	9	
Vomiting			
subjects affected / exposed	21 / 101 (20.79%)	33 / 99 (33.33%)	
occurrences (all)	48	61	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	15 / 101 (14.85%)	8 / 99 (8.08%)	
occurrences (all)	20	10	
Dry skin			
subjects affected / exposed	8 / 101 (7.92%)	9 / 99 (9.09%)	
occurrences (all)	11	9	
Petechiae			
subjects affected / exposed	18 / 101 (17.82%)	11 / 99 (11.11%)	
occurrences (all)	28	12	
Pruritus			
subjects affected / exposed	15 / 101 (14.85%)	11 / 99 (11.11%)	
occurrences (all)	17	23	
Rash			
subjects affected / exposed	5 / 101 (4.95%)	14 / 99 (14.14%)	
occurrences (all)	7	24	
Rash maculo-papular			
subjects affected / exposed	17 / 101 (16.83%)	19 / 99 (19.19%)	
occurrences (all)	25	35	
Skin disorder			
subjects affected / exposed	14 / 101 (13.86%)	16 / 99 (16.16%)	
occurrences (all)	21	30	
Renal and urinary disorders			
Fluid retention			
subjects affected / exposed	34 / 101 (33.66%)	41 / 99 (41.41%)	
occurrences (all)	69	78	
Renal disorder			
subjects affected / exposed	7 / 101 (6.93%)	4 / 99 (4.04%)	
occurrences (all)	9	4	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	21 / 101 (20.79%)	11 / 99 (11.11%)	
occurrences (all)	26	20	
Bone pain			
subjects affected / exposed	8 / 101 (7.92%)	9 / 99 (9.09%)	
occurrences (all)	13	13	
Musculoskeletal disorder			
subjects affected / exposed	6 / 101 (5.94%)	6 / 99 (6.06%)	
occurrences (all)	7	10	
Myalgia			
subjects affected / exposed	4 / 101 (3.96%)	8 / 99 (8.08%)	
occurrences (all)	4	12	
Pain in extremity			
subjects affected / exposed	18 / 101 (17.82%)	17 / 99 (17.17%)	
occurrences (all)	26	32	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 101 (2.97%)	10 / 99 (10.10%)	
occurrences (all)	4	21	
Device related infection			
subjects affected / exposed	19 / 101 (18.81%)	12 / 99 (12.12%)	
occurrences (all)	22	16	
Enterocolitis infectious			
subjects affected / exposed	5 / 101 (4.95%)	9 / 99 (9.09%)	
occurrences (all)	6	12	
Infection			
subjects affected / exposed	44 / 101 (43.56%)	44 / 99 (44.44%)	
occurrences (all)	82	93	
Lip infection			
subjects affected / exposed	7 / 101 (6.93%)	8 / 99 (8.08%)	
occurrences (all)	9	14	
Mucosal infection			
subjects affected / exposed	6 / 101 (5.94%)	8 / 99 (8.08%)	
occurrences (all)	8	13	
Pneumonia			

subjects affected / exposed	19 / 101 (18.81%)	31 / 99 (31.31%)	
occurrences (all)	22	44	
Rash pustular			
subjects affected / exposed	5 / 101 (4.95%)	9 / 99 (9.09%)	
occurrences (all)	5	23	
Sepsis			
subjects affected / exposed	9 / 101 (8.91%)	14 / 99 (14.14%)	
occurrences (all)	10	18	
Skin infection			
subjects affected / exposed	11 / 101 (10.89%)	12 / 99 (12.12%)	
occurrences (all)	17	21	
Urinary tract infection			
subjects affected / exposed	10 / 101 (9.90%)	15 / 99 (15.15%)	
occurrences (all)	15	21	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 101 (14.85%)	17 / 99 (17.17%)	
occurrences (all)	24	33	
Hyperuricaemia			
subjects affected / exposed	17 / 101 (16.83%)	13 / 99 (13.13%)	
occurrences (all)	29	23	
Hypoalbuminaemia			
subjects affected / exposed	6 / 101 (5.94%)	14 / 99 (14.14%)	
occurrences (all)	7	21	
Hypomagnesaemia			
subjects affected / exposed	9 / 101 (8.91%)	3 / 99 (3.03%)	
occurrences (all)	10	3	
Hypophosphataemia			
subjects affected / exposed	5 / 101 (4.95%)	6 / 99 (6.06%)	
occurrences (all)	5	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2015	Amendment No. 1 (dated 23 June 2015) to the protocol was issued after 17 patients were enrolled. The following major procedural changes (not all-inclusive) were made to the protocol: • Add medications restricted during the treatment with dasatinib • Add supportive care medications • Include some minor administrative-type changes
15 June 2016	Amendment No. 2 (dated 15 June 2016) to the protocol was issued after 48 patients were enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: • Integration of the Safety Update Letter • Adjustment of the duration of the clinical trial • Update of the Serious Advese Events • Update of the prophylaxis with dexamethasone • Include some minor administrative-type changes/ Changes in the personal responsibility
19 March 2019	Amendment No. 3 (dated 19 March 2019) to the protocol was issued after 151 patients were enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: • Adjustment of study duration and decrease of sample size from 277 to 203 patients due to slow recruitment • Adjustment of standard chemotherapy as a result of reported delivery shortages of Daunorubicin -> Integration of Idarubicin which can be used in case Daunorubicin is not available • Adaption of Informed Consent Form on the General Data Protection Regulation (EU)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported